Fibrodysplasia ossificans progressiva: Report of two cases

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ABSTRACT

Fibrodysplasia Ossificans Progressiva (FOP) is a rare hereditary connective tissue disease, genetically inherited as an autosomal dominant trait with complete penetrance but variable expressivity. Onset is typically in childhood and progressive involvement of the spine and proximal extremities leads to immobility and articular dysfunction. We present two cases with the typical features of FOP and a review of the pathogenesis, clinical manifestations and treatment options of this rare disease.

Introduction

The first report of a patient with a probable Fibrodysplasia Ossificans Progressiva (FOP) dates from 1692, when Gui Patin described a woman that gradually became “dure comme du bois” (1). In 1868 Von Dusch used for the first time the expression Myositis Ossificans Progressiva (2) and a year later Munchmeyer made the classic description of this disease, which is also known by this author’s name. Recently the preferred designation for this disorder has changed to FOP as it reflects with more accuracy the pathophysiology of the disease (3). FOP is a rare hereditary disorder, occurring in 0.61 cases in 1 million persons (4), with an autosomal dominant nature and variable expression of the presumed defective gene (5,6). As most patients do not have a past familial history of FOP it is assumed that frequently the disease occurs as the result of a new sporadic mutation (7,8). The clinical expression of the disease is characterised by an ectopic endochondral ossification of connective tissue and striated muscles, beginning in the upper paraspinal muscles and spreading from axial to appendicular, cranial to caudal, and proximal to distal sites, leading to the development of the “stone man”, a syndrome described in less than 600 cases in the literature (9). We present two cases with the typical features of FOP and review the pathogenesis, clinical manifestations and treatment options of this rare disease.

Case reports

Case 1

A 2-year-old caucasian boy presented with progressive loss of range of motion of his right elbow, after a fall at the age of 18 months. Two weeks later he developed cervical oedema, without pain or inflammatory signs, and 4 months later hard posterior cervical masses appeared, associated with a hard mass in the left elbow and fixed flexed deformity. Over the next 10 years the disease remained stable, but at the age of 12 he developed right knee oedema, again without inflammatory signs. Five years later he noticed oedema of the left knee and hard masses in the posterior aspect of the knee with fixed flexed deformity. By this time he also developed a lung abscess in the left upper lobe (without infective agent isolated), which was treated with netilmicin and cephradin.

The patient was a heavy smoker and had a low social and economic status. The past medical familial history was not significant. He had 5 healthy brothers. Physical examination showed a blood pressure of 105/80 mmHg and a heart rate of 88 beats/min. He was 1.51 m tall and weighed 32 Kg. Dentition was poor, and the incisor to incisor distance was 1 cm. He had hard masses in the chest and a chest expansion of 1 cm. Cardiac and abdominal examinations were unremarkable. Musculoskeletal examination depicted absent movement of the neck, thoracic and lumbar dextroscoliosis with paraspinal hard masses, markedly diminished motion of the shoulders and hips in all planes and fixed flexed elbows at 90°. The left knee presented a fixed flexed posture at 90° and the right knee had limited range of motion. There were shortened first metatarsals of both feet. Routine laboratory evaluation was normal. Pulmonary function testing revealed restrictive lung disease with a normal diffusion capacity.

Radiographs of the spine showed extensive paraspinal ossification and thoracolumbar scoliosis. The shoulders and elbows presented juxta-articular ossification, particularly on the right side. Both hips showed deformity and juxta-articular ossification, with bridges across the right hip resulting in ankylosis and ossification of the left adductors determining adduction deformity of the left hip. On the upper third of the tibial medial aspect there was ossification of the pos-


**Case Report**

Fibrodysplasia ossificans progressiva / J.E. Fonseca et al.

The muscle biopsy was performed over a hard muscular mass and showed nodular ossification areas surrounded by fibrous connective tissue and atrophic muscle with increased collagen fibres in the interstitial connective tissue.

The patient abandoned the outpatient clinic, did not complete the prescribed therapy (etidronate), and died of pneumonia one year after the diagnosis.

**Case 2**

A caucasian girl presented at the age of 2 years with an inflammatory nodule in the proximal aspect of her upper left limb. During the following 5 years she had several episodes of upper left limb pain, with progressive loss of range of motion of her left shoulder and elbow. After that and up to her 17th year she developed similar complaints in her right upper limb and also in the cervical spine.

At the age of 17 years she had an acute episode of pain and swelling of the proximal aspect of her lower left limb, spreading during the following month to the distal part of the limb. A month later the same process took place on the other lower limb. Over the next year she lost gradually the normal range of motion of her knees and hips. The disease was persistently active for the next 8 years with recurrent episodes of painful swollen nodules in the limbs, usually after minor trauma, and progressive loss of distance between the incisors. At the age of 25 an acute inflammatory cervical mass appeared, causing difficulty in swallowing. She underwent surgery for removal of the mass (which was found to be made of muscle, fibrous tissue and bone) and to increase the jaw mobility. During the last 4 years she has had only sporadic inflammatory nodules, without further deterioration of her joint mobility.

The past medical and familial history were not significant. Physical examination showed a blood pressure of 120/80 mmHg and a heart rate of 80 beats/min. She was 1.56 m tall and weighed 57 Kg. Dentition was poor, the incisor to incisor distance was 2 cm. She had a chest expansion of 1.5 cm. Cardiac and abdominal examinations were unremarkable. Musculoskeletal examination detected spinal ankylosis and thoracic and lumbar dextroscoliosis with paraspinal hard masses. There was ankylosis of the right shoulder, left elbow (at 70° flexion) and of both hips. The left shoulder had markedly diminished motion (0° adduction and 30° abduction, 20° flexion and 10° extension, internal rotation of 80-120°). The right elbow had a flexion range of 70 to 120°. The left knee presented flexion possible between 5° and 30° and the right knee between 0° and 20°. The first metatarsals of both feet were shortened.

Routine laboratory evaluation was normal. Pulmonary function testing revealed restrictive lung disease with a normal diffusion capacity.

Radiographs of the spine showed fusion of the cervical vertebral bodies (Fig. 1a), extensive para-vertebral ligament ossification (Fig. 1a) and thoraco-lumbar dextroscoliosis (Fig. 1b). The shoulders and elbows presented juxta-articular ossification with bridges across the joints. Both hips showed deformity and juxta-articular ossification, with bridges across the joints resulting in ankylosis (Fig. 2). There was also a generalised low bone density.

At the age of 7 she underwent a deltoid

Fig. 1. (a) Fusion of cervical vertebral bodies and extensive para-vertebral ligament calcification; (b) thoraco-lumbar dextroscoliosis.
muscular biopsy that was normal. She did not repeat the biopsy as the diagnosis became obvious on clinical grounds. During the last 4 years the patient has been treated with etidronate sodium 400 mg/day (10/mg/Kg/day) with apparent adequate control of the disease. No further functional deterioration occurred in the jaw joint after surgery.

Discussion
The clinical presentation of FOP is variable but most patients have onset of soft tissue calcification by the age of 10, 50% before the first 2 years of life (as was the case of our 2 patients), with a mean age of onset of 3.6 years (10, 11). Ectopic ossification begins in the upper paraspinal muscles, often causing inflammatory signs, painful masses, hardening of periarticular tissues and progressive loss of joint function (12). The disease progresses from axial to appendicular, cranial to caudal, and proximal to distal sites (13, 14). This characteristic pattern of the disease course was observed in our 2 cases. The clinical expression of FOP may cause the fusion of the costochondral joints, which leads to restrictive lung disease and increases the risk of pneumonia, two main causes of morbidity and mortality (15,16) as in fact our first case dramatically demonstrated. Routine laboratory evaluation is generally normal, although slight increases in the sedimentation rate may occur during acute inflammatory episodes. Radiographs not only show the periarticular calcifications and joint ankylosis but also depict some congenital anomalies. The most frequent finding is microdactyly, particularly of the first toes, which is present in 75 to 90% of patients. Other abnormalities include hypoplasia and fusion of the digits, shortened metatarsals and metacarpals, hallux valgus deformity, clinodactyly, shallow acetabula, widened femoral necks and spina bifida (12). Both of our patients had microdactyly of the first toes and the second patient had probably a shallow acetabula. The histopathologic features of FOP undergo variation during the course of the disease, and are only present in the affected anatomic areas. This focal and time-dependent behaviour explains the normal muscle biopsy of our second patient, which was done in a precocious phase and probably in an unaffected area. Early lesions show lymphocytes, macrophages and fibroblasts which later evolve into areas of connective tissue with an ossification centre, where osteoblasts, osteocytes and osteoclasts can be observed (17-20).

Recently the dramatic overexpression of bone morphogenetic protein (BMP) 4, an osteogenic morphogen, has been identified in the lymphocytes of patients with FOP and also in cells derived from early fibroproliferative lesions (21). The gene for the protein BMP 4 has been mapped to chromosome 14q22-q23 (22) and obviously the demonstration of mutations in the gene, particularly in its promoter sequence, would be evidence in favour of a key role for this gene in the clinical expression of FOP. On the other hand, the extra-cellular domain of the BMP receptor has a high affinity for BMP 4, which raises the possibility of using BMP receptor therapy in FOP (23).

To date there has been no convincing evidence that any treatment is able to change the progress of FOP. Several studies using calcium binding, parathyroid extract and vitamin D showed that these drugs do not affect the course of disease (25, 26). Isotretinoin in a dose of 1 to 2 mg/Kg/day reduces ectopic ossification, but unfortunately may induce growth arrest, dense metaphyseal bands and calcification of the enthesis (27). Another theoretically attractive approach is the use of ascorbic acid, which may modify calcium transport and thus reduce calcification, but evidence for the effectiveness of this treatment option is scarce (28). Corticosteroids may be helpful for acute inflammatory episodes, although there is no evidence that they suppress the ectopic ossification (3). In fact, the only promising drug appears to be etidronate, which in doses from 10 to 30 mg/Kg/day reduces ectopic ossification, being particularly useful for the control of post-operative heterotopic ossification. However, high doses of etidronate taken for long periods of time may induce a mineralization defect, fractures and muscle weakness. As short-term treatment with etidronate is not associated with these complications, probably this drug should be used as an intermittent treatment (29).

In our second patient the use of etidronate appeared to be helpful in the control of new ectopic ossification. Finally the option of surgery should be regarded with great caution as the disease is characteristically exacerbated after surgery (30) and also because of anaesthetic dif-
CASE REPORT

Facilities caused by cervical spinal ankylosis and restrictive pulmonary disease. Nevertheless our second case suggests that in very severe cases and with concomitant etidronate treatment surgery may be successful and reasonably safe.

References